Claims

We claim:

1. A method of inhibiting endothelial cell growth, comprising contacting endothelial cells with a pharmaceutical composition comprising at least one protein selected from the group consisting of:

(a) therapeutically effective fragments of calreticulin;

(b) therapeutically effective variants of calreticulin;

(c) calreticulin; and

(d) therapeutically effective variants of the fragments of (a).

2. The method of claim 1 wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

3. The method of claim 1 wherein the therapeutically effective fragment of calreticulin comprises a polypeptide of about 180 amino acids from the N-terminus of calreticulin.

4. The method of claim 1 wherein the therapeutically effective fragment of calreticulin consists essentially of an amino acid sequence selected from the group consisting of:

(a) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 3;

(b) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 4;

(c) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 5;

(d) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 6;

(e) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 8; and

f) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 9.

5. A method of inhibiting angiogenesis in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition comprising at least one protein selected from the group consisting of:

(a) therapeutically effective fragments of calreticulin;

(b) therapeutically effective variants of calreticulin;

(c) calreticulin; and

(d) therapeutically effective variants of the fragments of (a).

6. The method of claim 5 wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

7. The method of claim 5 wherein the therapeutically effective fragment of calreticulin comprises a polypeptide of about 180 amino acids from the N-terminus of calreticulin.

8. The method of claim 5 wherein the therapeutically effective fragment of calreticulin consists essentially of an amino acid sequence selected from the group consisting of:

(a) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 3;

(b) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 4;

(c) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 5;

(d) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 6;

(e) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 8; and

f) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 9.

9. The method of claim 5 wherein the angiogenesis is associated with a disease, other than a tumor, that is associated with neovascularization.

10. The method of claim 9 wherein angiogenesis is inhibited in a disease selected from a group consisting of diabetic retinopathy, retrolental fibroplasia, trachoma, neovascular glaucoma, psoriasis, angiofibromas, immune-inflammation, atherosclerosis, excessive wound repair, retinal neovascularization, macular degeneration, corneal graft rejection, contact lens overwear, Crohn's disease and non-immune inflammation.

11. The method of claim 9 wherein the disease is selected from a group consisting of rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, Goodpasture's Syndrome, systemic vasculitis, scleroderma, Sjogren's syndrome, sarcoidosis and primary biliary cirrhosis.

12. A method of treatment of Kaposi's sarcoma, comprising administering to the subject an effective amount of pharmaceutical composition comprising at least one protein selected from the group consisting of:

(a) therapeutically effective fragments of calreticulin;

(b) therapeutically effective variants of calreticulin.

(c) calreticulin; and

(d) therapeutically effective variants of the fragments of (a).

13. The method of claim 5 further comprising providing a second anti-angiogenic agent selected from a group consisting of platelet-factor-4, IP-10 (interferon (IFN)-γ inducible protein-10), MIG (Monokine induced by IFN-γ), INF-γ, IFN-α, angiostatin, endostatin, fumagillin, AGM-1470, thrombospondin, a fragment of prolactin, antibody against the integrin $\alpha_v\beta_3$, IL-12, cleaved conformation of the serpin antithrombin, thalidomide, and mixtures thereof.

14. The method of claim 5 further comprising administering a chemotherapeutic agent.

15. The method of claim 5 further comprising administering a hormone.

16. The method of claim 5 further comprising administering an anti-inflamatory agent.

17. The method of claim 5 further comprising administering an anti-viral agent.

18. The method of claim 5 wherein the angiogenesis is inhibited in pregnancy.

19. The method of claim 5 wherein the angiogenesis is inhibited to terminate pregnancy.

20. The method of claim 5 wherein the angiogenesis is inhibited in periodontal disease.

21. The method of claim 20 further comprising administering an antibiotic.

22. The method of claim 5 wherein the angiogenesis is inhibited in radiation induced injury.

23. The method of claim 5 wherein the angiogenesis is inhibited in chemotherapy induced injury.

24. The method of claim 5 wherein the pharmaceutical composition inhibits angiogenesis which is stimulated by an angiogenesis inducer selected from a group consisting of, basic fibroblast growth factor, acidic fibroblast growth factor, Vascular Endothelial Growth Factor (VEGF), hepatocyte growth factor, Interleukin (IL)-15, IL-8, platelet-derived endothelial cell growth factor (PDECGF), Transforming Growth Factor (TGF)-β, Tumor necrosis Factor (TNF)α, angiogenin, Cripto, and mixtures thereof.

25. The method of claim 5, wherein the subject is immunocompromized due to T-lymphocyte deficiency.

26. A method of inhibiting tumor growth, comprising contacting tumor cells with an effective amount of a pharmaceutical composition comprising at least one protein selected from the group consisting of:

(a) therapeutically effective fragments of calreticulin;

(b) therapeutically effective variants of calreticulin;

(c) calreticulin; and

(d) therapeutically effective variants of the fragments of (a).

27. The method of claim 26 wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

28. The method of claim 26 wherein the therapeutically effective fragment of calreticulin comprises a polypeptide of about 180 amino acids from the N-terminus of calreticulin.

29. The method of claim 26 wherein the therapeutically effective fragment of calreticulin consists essentially of an amino acid sequence selected from the group consisting of:

(a) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 4;

(b) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 5;

(c) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 6;

(d) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 8; and

(e) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 9.

30. The method of claim 26 wherein the tumor growth occurs in a subject and is inhibited by administering to the subject an effective amount of the pharmaceutical composition.

31. A protein consisting essentially of an amino acid sequence selected from the group consisting of:

(a) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 4;

(b) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 5;

(c) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 6;

(d) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 8; and

(e) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 9.

32. A composition comprising a protein according to claim 31, and a pharmaceutically acceptable carrier.

33. A vector comprising a nucleotide sequence encoding a protein with an amino acid sequence selected from the group consisting of:

(a) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 3;

(b) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 4;

(c) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 5;

(d) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 6;

(e) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 8; and

f) at least 5 contiguous amino acid residues of the sequence shown in Seq. I.D. No. 9.

34. A host cell comprising the vector according to claim 33.

35. A method of isolating a therapeutically effective fragment of calreticulin from a sample comprising:

(a) contacting the sample with at least one peptide where the peptide has the amino acid sequence selected from the group consisting of Seq. I.D. No. 10 and Seq. I.D. No. 11;

(b) recovering the portion of the sample that does not bind to the peptide; and

(c) assaying the recovered portion of the sample for therapeutic activity.

36. A therapeutically effective fragment of calreticulin identified by the method of claim 35.

37. A vector comprising a nucleotide sequence encoding the therapeutically effective fragment of claim 36.

38. A host cell comprising the vector according to claim 37.

39. A method of isolating a therapeutically effective variant of calreticulin from a sample comprising:

(a) contacting the sample with at least one peptide where the peptide has the amino acid sequence selected from the group consisting of Seq. I.D. No. 10 and Seq. I.D. No. 11;

(b) recovering the portion of the sample that does not bind to the peptide; and

(c) assaying the recovered portion of the sample for therapeutic activity.

40. A therapeutically effective variant of calreticulin identified by the method of claim 39.

41. A vector comprising a nucleotide sequence encoding the therapeutically effective variant of claim 40.

42. A host cell comprising the vector according to claim 41.

43. A therapeutically effective fragment of calreticulin that:

(a) does not bind to the amino acid sequence shown in Seq. I.D. No. 10; and

(b) displays a biological activity selected from the group consisting of: at least 30% inhibition of angiogenesis, at least 30% inhibition of tumor growth, and at least 30% inhibition of endothelial cell growth.

44. The therapeutically effective fragment of claim 43, wherein the biological activity is selected from the group consisting of: at least 40% inhibition of angiogenesis, at least 40% inhibition of tumor growth, and at least 40% inhibition of endothelial cell growth.

45. A vector comprising a nucleotide sequence encoding the therapeutically effective fragment of claim 43.

46. A host cell comprising the vector according to claim 45.

47. A therapeutically effective variant of calreticulin that:

(a) does not bind to the amino acid sequence shown in Seq. I.D. No. 10; and

(b) displays a biological activity selected from the group consisting of: at least 30% inhibition of angiogenesis, at least 30% inhibition of tumor growth, and at least 30% inhibition of endothelial cell growth.

48. The therapeutically effective fragment of claim 42, wherein the biological activity is selected from the group consisting of: at least 40% inhibition of angiogenesis, at least 40% inhibition of tumor growth, and at least 40% inhibition of endothelial cell growth.

49. A vector comprising a nucleotide sequence encoding the therapeutically effective variant of claim 47.

50. A host cell comprising the vector according to claim 49.

51. A mimetic of the protein of claim 31.

52. A mimetic of the therapeutically effective fragment of claim 36.

53. A mimetic of the therapeutically effective variant of claim 40.

54. A mimetic of the therapeutically effective fragment of claim 43.

55. A mimetic of the therapeutically effective variant of claim 47.

56. The method of claim 5 further comprising administering radiation therapy.